

Detailed information on the project

Title of project	Musical and psychomotor interventions for cognitive, sensorimotor, and cerebral decline in patients with Mild Cognitive Impairment (COPE): a study protocol for a multicentric randomized controlled study
Language of project	English
Contributing institutions	<ul style="list-style-type: none"> ▪ University of Applied Sciences and Arts Western Switzerland HES-SO <ul style="list-style-type: none"> - Geneva School of Health Sciences (Host Institution of the Principal Investigator) (HEdS-GE) - Geneva School of Social Work (HETS-GE) ▪ University of Geneva <ul style="list-style-type: none"> - Faculty of Psychology and Educational Sciences - Faculty of Medicine ▪ University Hospitals of Geneva (HUG) <ul style="list-style-type: none"> - Memory Center ▪ Lausanne University Hospital (CHUV) <ul style="list-style-type: none"> - Leenaards Memory Center
Key words	Mild cognitive impairment; Randomized controlled trial; Non-medical interventions; Music instrumental practice; Psychomotor therapy; Passive control group; Cognitive performance; Sensorimotor performance; Well-being; Autonomy; Experience induced functional and structural brain plasticity; Multivariate data-driven analyses
Geographical space	Geneva, Switzerland
Research question	Can 6 months of active music practice vs. psychomotor interventions in MCI (Mild Cognitive Impairment) patients impact positively cognitive and sensorimotor performance as well as associated brain plasticity compared to a passive control group of healthy matched individuals?
Aim of project	This RCT aims to determine if two specifically developed innovative non-medical experimental interventions over six months, i.e. intensive musical instrumental practice and psychomotor interventions in small groups may have an important societal impact, via the reduction or stabilization of cognitive, sensorimotor and cerebral decline, in MCI patients compared to a passive control group of healthy matched controls, and to each other.
Methods	<p>Randomized Controlled Trial; Large Behavioral battery (cognitive and sensorimotor tasks); Brain imaging battery (structural and functional MRI (Magnetic Resonance Imaging)). Two interventions: Music Practice, Psychomotor practice: 2 times per week 45 minutes, ~40 courses/~6 months. Compared to a passive matched healthy control group. Uni & multivariate analyses.</p> <p>Population We recruited community-dwelling older adults with an MCI diagnosis from a University Memory Clinic (HUG & CHUV). Originally, we planned the study to have an equal number of patients in both experimental groups and in the passive control group (n=16 for each group). However, due to the COVID pandemic and typical attrition in this vulnerable population (diagnoses of Alzheimer's, brain abnormalities, accidents, inability to continue attending two</p>

	<p>sessions per week, etc.), the final numbers changed. Ultimately, 11 patients completed the full protocol in the music group, 10 in the psychomotor group, and we recruited 16 healthy matched controls for the passive control group.</p> <p>For details we refer to the published protocol: https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-022-03678-0</p>
Relevance	<p>At present, the only conclusion from clinical and translational research is that dementia is not curable. Despite great progress made in the early detection and, consequently, in the delay and reduction of symptoms, the progression of the disease, once started, is irreversible. This is why approaches that can delay, diminish or even temporarily overcome brain decline, especially at early stages, are of crucial importance. We intend to reverse the slope of decline in the fragile and neglected MCI population via intensive non-medical interventions, preventing or retarding the development of dementia.</p>
Results	<p>Post-intervention Behavioral Results: We found several specific improvements in the two experimental patient groups after six months of twice-weekly interventions. Direct comparison between the two experimental groups, showed greater improvement for verbal semantic fluency in the music practice intervention group. Verbal fluency may reflect cognitive impairment, and involves, apart from lexical semantic retrieval, elements of working memory, attention, and cognitive flexibility (switching). Therefore, it is considered a component of executive functions. For the laterality recognition test, in which participants assess right/left judgments of body parts presented by photos on a computer, evaluating the representation of the body schema, the psychomotor intervention group showed stronger learning for awareness of feet laterality post-intervention. Awareness of the body schema is linked to cognitive function and may lower the increased fall risk found in MCI patients. Both statistically significant observations confirm our initial hypotheses.</p> <p>When comparing each group, music practice intervention, psychomotor intervention, and healthy controls over time (6 months versus baseline), thus investigating <i>progress</i> in each group separately, verbal short-term memory improved statistically significantly in the music practice intervention and in the control group, but not in the psychomotor intervention group. Verbal fluency only improved significantly exclusively in the music practice group, not in the control group, which indicates an intervention effect and not a test-retest effect. Then, speech in noise perception also exclusively improved in the music practice group. The ability to understand speech in background noise is a common challenge in daily communication, especially among the elderly. This difficulty can lead to social isolation, reduced quality of life, and cognitive decline. Right-hand dexterity also improved only in the music group. In contrast, the unilateral balance test, holding on one leg, improved for the left leg exclusively in the psychomotor group. In the same vein, the awareness of feet laterality showed improvement in the psychomotor group only. Both latter results may diminish fall risk and increase mobility and autonomy. Again, all these statistically significant results over time are plausible and go in the direction of our hypotheses.</p>

Finally, on the behavioral level, we observe that all advantages for the intervention groups relate to **activities of daily life**: speech in noise perception, verbal fluency, manual dexterity, and body balance and awareness. Several studies could relate such advantages in the context of music training to brain changes in healthy older adults. We hope to confirm such associations by our future analyses.

Post-intervention Brain Imaging Results and Associations with Behavior.
Analyses are ongoing.

Pre-intervention" "baseline" Behavioral and Brain Imaging Results, comparing MCI Patients to Matched Healthy Controls

Behavior: At baseline, we compared behavioral and cognitive neuroimaging data between patients with Mild Cognitive Impairment (MCI) and healthy controls. **Understanding MCI and Alzheimer's disease's underlying mechanisms for diagnosis and potential biomarkers is crucial.** Behaviorally, we assessed differences in 7 tests and 1 questionnaire, using Bonferroni correction. **Patients showed poorer performance than healthy controls in 4 tests:** the COGTEL (general cognition), trail making (visual attention, speed, flexibility), D2 (visual attention, speed), and binaural speech in noise (auditory attention). These findings validate our MCI test battery and patient group.

Brain-wise, we conducted two baseline analyses. First, **seed-based functional connectivity** assessed connectivity with specific brain regions, revealing **decreased brain connectivity in MCI patients compared to healthy controls** for 3 out of 9 seeds. Notably, the left inferior temporal gyrus connectivity reduction holds promise due to its size, importance for memory and executive functions, and overlap with grey matter changes. Especially music training taps into executive functions.

Voxel-based morphometry highlighted **widespread grey matter decrease in MCI patients compared to controls**, especially in medial temporal lobe, hippocampus, amygdala, and cerebellum. While medial temporal findings align with the literature, significant cerebellum and inferior frontal reductions offer novel insights. These findings may correlate with behavior and functional connectivity. Investigating such inter related changes after the interventions could reveal protective plasticity. In another study, we could show that cerebellum increase in healthy elderly related to improved verbal memory after music training (<https://www.sciencedirect.com/science/article/pii/S2666956023000119>), and to better conserved white microstructure in the fornix that links both hippocampi (<https://www.frontiersin.org/articles/10.3389/fnagi.2022.817889/full>).

Our approach, merging MRI and behavior, may illuminate MCI pathophysiology. Furthermore, this approach could offer insights into strategies to delay or mitigate the onset of Alzheimer's disease among individuals diagnosed with MCI.

Conclusion

Preliminary conclusion

	Evidence-based ecological low-cost and attractive interventions like music practice and psychomotor training in small groups are promising venues to improve cognitive function and body control in MCI patients, re-integrating them into society and thus increasing their well-being and that of their relatives.
Project lead	Prof. Dr. Clara James, PhD in neuroscience, MSc in experimental psychology, & professional musician, expert in the impact of music practice on brain and behavior, https://orcid.org/0000-0001-7480-0682
Project team	<ul style="list-style-type: none"> - Dr. Damien Marie, co-applicant, PhD in neuroscience, MSc in biology, expert in advanced MRI (Magnetic Resonance Imaging) brain recording & analyses - Cyrille Stucker, Antonio M. Fernandes, scientific collaborators, MSc in clinical psychology - Prof. Dr. Chantal Junker-Tschopp, PhD in psychology and psychomotor expert - Consultants: <ul style="list-style-type: none"> - Prof. Dr. Giovanni Frisoni, expert in cognitive decline and dementia - Prof. Dr. Matthias Kliegel, expert in cognitive aging - Dr. Dr. Andrea Brioschi Guevara, neuropsychologist - Prof. Dr. Isabelle Mili, expert in music didactics
Mandating institutions	Geneva School of Health Sciences, University of Applied Sciences and Arts Western Switzerland HES-SO / Haute école de santé de Genève HES-SO
URL of project	https://www.hesge.ch/heds/rad/projets/contrecarrer-declin-cognitif-sensorimoteur-cerebral-chez-les-patients-atteints-troubles
Start and End of project	Planned start: Mai 2020. Due to the Corona pandemic, the 6-month interventions started in February 2021 instead of September 2020 at the Memory Center of the University Hospitals and University of Geneva, with a reduced group of patients. We then conducted two more waves at the Leenaards Memory Center, Lausanne University Hospital, ending data collection end of March 2023.
Dissemination	<p>Publications: The protocol was published in BMC Geriatrics an Open Access Journal with an Impact Factor of 4.1: https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-022-03678-0</p> <p>Oral presentations:</p> <p>The project was presented at the Leenaards Memory Center of the Lausanne University Hospital on May 2, 2022: “Déclin neurocognitif léger : entraînement musical et psychomotricité, des interventions prometteuses?”</p> <p>The project was presented at the Center for Biomedical Imaging of the University of Geneva at June 26, 2023 “Countervail mild cognitive impairment with music/psychomotor training, preliminary results”.</p> <p>We will present the results at the Brain Imaging meeting in Champéry Switzerland January 7-11, 2024, and at the Human Brain Mapping Conference June 23-27, 2024 in Seoul, Korea</p> <p>Foreseen Results publications:</p>

1. One on brain and behavioral differences between MCI patients and healthy controls at baseline, for instance in the international journal "Annals of Neurology". *Foreseen fall 2023.*
2. Another on behavioral results after 6 months of interventions for instance in the international journal "Alzheimer's Research & Therapy" *Foreseen spring 2024.*
3. A third on grey matter plasticity in association with behavioral results for instance in the international journal "NeuroImage: Clinical" *Foreseen fall 2024.*
4. And finally, a paper on functional connectivity in association with behavioral results for instance in the international journal "Brain" *Foreseen fall 2024.*

Other foreseen communications:

In professional journals intended for a non-academic audience and in newspapers - Presentations at elderly and community centers (Connaissance 3) - Dissemination of results in psychology, neuroscience and medicine curricula at the University of Geneva - Communicate the main results to the general public and the local and federal politics